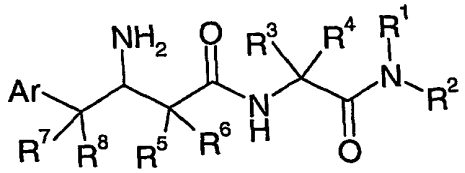
Claims

1. A compound of formula (I) or a pharmaceutically-acceptable salt thereof,



(I)

wherein:

Ar is phenyl optionally substituted with 1, 2, 3, 4 or 5 groups independently selected from R^9;

R^9 is selected from halo, (1-6C)alkyl (optionally substituted with 1-5 halo), (1-6C)alkoxy (optionally substituted with 1-5 halo) and cyano;

R^1 is selected from hydrogen and (1-6C)alkyl;

R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkylHET1, -(1-6C)alkylHET2, -(1-6C)alkylCO$_2$(1-6C)alkyl, -(1-6C)alkylCO$_2$(3-8C)cycloalkyl, -(1-6C)alkylCO$_2$AR1, -(1-6C)alkylCO$_2$HET1, -(1-6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1, -(1-6C)alkylOCOHET1, -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1, -(1-6C)alkylCOHET1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl, -(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl , -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl, -(1-6C)alkylSO$_2$NH(1-6C)alkyl, -(1-6C)alkylSO$_2$ (1-6C)alkyl, -SO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$N-di(1-6C)alkyl;

or

R^1 and R^2 may together with the nitrogen to which they are attached form a ring defined by HET1 or HET3; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-

6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, –CO_2(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl, (3-8C)cycloalkenyl, (5-12C)bicycloalkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, AR1, AR2, HET1, HET2, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1, and -(1-6C)alkylHET2; or

R^3 and R^4 together form a ring as defined by (3-8C)cycloalkyl, AR2, HET1 or HET2;

R^5, R^6, R^7 and R^8 are independently selected from hydrogen and (1-6C)alkyl;

wherein any (1-6C)alkyl group within any definition of R^1, R^2, R^3, R^4, R^5, R^6, R^7 or R^8 is optionally substituted by 1 or 2 substituents independently selected from hydroxy and fluoro;

wherein any (3-8C)cycloalkyl, (3-8C)cycloalkenyl, (5-12C)bicycloalkyl or (6-12C)tricycloalkyl within any definition of R^2, R^3 or R^4 is optionally substituted;

AR1 is optionally substituted phenyl;

AR2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic carbocylic ring;

HET1 is an optionally substituted 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised, and wherein any available carbon, sulfur or nitrogen atom may be oxidised;

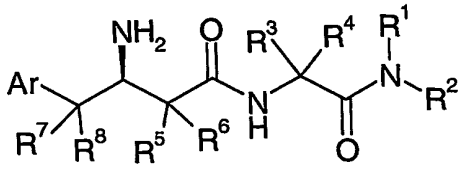
HET2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

HET3 is an N-linked saturated bicyclic or tricyclic ring system, containing up to 12 ring atoms including the linking nitrogen atom;

wherein suitable optional substituents on (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from phenyl (optionally substituted with halo, trifluoromethyl, (1-4C)alkyl or (1-4C)alkoxy)), halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, -$CONH_2$,

–CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-SO_2$(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2NH$(1-6C)alkyl, $-SO_2N$di(1-6C)alkyl and $–NHSO_2$(1-6C)alkyl.

2. A compound as claimed in Claim 1 which is a compound of the formula (IA)



(IA)

or a pharmaceutically acceptable salt thereof, wherein Ar, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 have any of the meanings defined in Claim 1.

3. A compound as claimed in Claim 1 or 2 or a pharmaceutically-acceptable salt thereof, wherein:

Ar is phenyl optionally substituted with 1, 2, 3, 4 or 5 groups independently selected from R^9;

R^9 is selected from halo, (1-6C)alkyl (optionally substituted with 1-5 halo), (1-6C)alkoxy (optionally substituted with 1-5 halo) and cyano;

R^1 is selected from hydrogen and (1-6C)alkyl;

R^2 is selected from hydrogen, (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkylHET1, -(1-6C)alkylHET2, -(1-6C)alkylCO_2(1-6C)alkyl, -(1-6C)alkylCO_2(3-8C)cycloalkyl, -(1-6C)alkylCO_2AR1, -(1-6C)alkylCO_2HET1, -(1-6C)alkylOCO(1-6C)alkyl, -(1-6C)alkylOCO(3-8C)cycloalkyl, -(1-6C)alkylOCOAR1, -(1-6C)alkylOCOHET1, -(1-6C)alkylCO(1-6C)alkyl, -(1-6C)alkylCO(3-8C)cycloalkyl, -(1-6C)alkylCOAR1, -(1-6C)alkylCOHET1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCO(3-8C)cycloalkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONH(3-8C)cycloalkyl, -(1-6C)alkylCON-di(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylN-di(1-6C)alkyl , -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkyl$NHSO_2$(1-6C)alkyl, -(1-6C)alkylSO_2NH(1-6C)alkyl, and -(1-6C)alkylSO_2N-di(1-6C)alkyl;

or

R^1 and R^2 may together with the nitrogen to which they are attached form a ring defined by HET1; wherein a ring comprising R^1 and R^2 is optionally substituted by 1 or 2 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, cyano, carboxy, carboxy(1-6C)alkyl, –CO(1-6C)alkyl, $–CO_2$(1-6C)alkyl, (1-6C)alkylamino, di-(1-6C)alkylamino, –NHCO(1-6C)alkyl, –CONH(1-6C)alkyl, -CONdi-(1-6C)alkyl and HET1;

R^3 and R^4 are independently selected from hydrogen, (1-6C)alkyl, -(1-6C)alkyl(3-8C)cycloalkyl, -(1-6C)alkyl(3-8C)cycloalkenyl, -(1-6C)alkylAR1, -(1-6C)alkylAR2, -(1-6C)alkylHET1, and -(1-6C)alkylHET2; or

R^3 and R^4 together form a ring as defined by (3-8C)cycloalkyl, AR2, HET1 or HET2;

R^5, R^6, R^7 and R^8 are independently selected from hydrogen and (1-6C)alkyl;

AR1 is optionally substituted phenyl;

AR2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic carbocylic ring;

HET1 is an optionally substituted 3-, 4-, 5- or 6-membered, unsaturated, partially or fully saturated monocyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), linked via a ring carbon atom, or a ring nitrogen atom if the ring is not thereby quaternised, and wherein any available carbon, sulfur or nitrogen atom may be oxidised;

HET2 is an optionally substituted 8-, 9- or 10-membered, unsaturated, partially or fully saturated bicyclic heterocyclyl ring containing up to four heteroatoms independently selected from O, N and S (but not containing any O-O, O-S or S-S bonds), and linked via a ring carbon atom in either of the rings comprising the bicyclic system;

wherein suitable optional substituents on AR1, AR2, HET1 and HET2 are 1, 2, 3, 4 or 5 substituents independently selected from halo, (1-6C)alkyl, halo(1-6C)alkyl, dihalo(1-6C)alkyl, trifluoromethyl, (1-6C)alkoxy, carboxy(1-6C)alkyl, carboxy(1-6C)alkoxy, hydroxy, amino, (1-6C)alkylamino, di(1-6C)alkylamino, $-CONH_2$, –CONH(1-6C)alkyl, -CONdi(1-6C)alkyl, –NHCO(1-6C)alkyl, $-S(O)_2NH_2$, $–SO_2$NH(1-6C)alkyl, $-SO_2$Ndi(1-6C)alkyl and –$NHSO_2$(1-6C)alkyl.

4. A compound of the formula (I) as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 and R^4 together form a ring as defined by AR2, HET1 or HET2; and

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

5. A compound of the formula (I) as claimed in Claim 1 or 2 or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl optionally substituted with 1 or 2 groups independently selected from R^9;

R^9 is selected from halo, methyl, methoxy and trifluoromethyl;

R^1 is hydrogen or methyl;

R^5 is hydrogen;

R^6 is hydrogen;

R^7 is hydrogen;

R^8 is hydrogen;

R^3 is hydrogen and R^4 is selected from -(1-4C)alkyl(3-8C)cycloalkyl, -(1-4C)alkyl(3-8C)cycloalkenyl, -(1-4C)alkylAR1, -(1-4C)alkylAR2, -(1-4C)alkylHET1 and -(1-4C)alkylHET2; and

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1, -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

6. A compound as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl substituted with 1, 2 or 3 fluoro;

R^1 is hydrogen;

R^2 is selected from (1-6C)alkyl, (3-8C)cycloalkyl , (5-12C)bicycloalkyl, (6-12C)tricycloalkyl, AR1, HET1, -(1-6C)alkylAR1, -(1-6C)alkylNHCO(1-6C)alkyl, -(1-6C)alkylNHCOAR1, -(1-6C)alkylCONH(1-6C)alkyl, -(1-6C)alkylCONHAR1, -(1-6C)alkylNH(1-6C)alkyl, -(1-6C)alkylNHAR1 and -(1-6C)alkylNH(HET1), -(1-6C)alkylNHSO$_2$(1-6C)alkyl and -(1-6C)alkylSO$_2$NH(1-6C)alkyl.

R^3 is hydrogen;

R^4 is CH_2-AR1, CH_2-HET1 or CH_2-HET2; and

R^5, R^6, R^7 and R^8 are all hydrogen.

7. A compound as claimed in Claim 1 or 2 or a pharmaceutically acceptable salt thereof wherein

Ar is phenyl substituted with 1, 2 or 3 fluoro;

R^1 is hydrogen;

R^2 is hydrogen, (1-4C)alkyl, -(1-4C)alkylAR1 or -(1-4C)alkylCONH(1-4C)alkyl;

R^3 is hydrogen;

R^4 is CH_2-AR1 or CH2-HET1; and

R^5, R^6, R^7 and R^8 are all hydrogen.

8. A compound as claimed in claim 5, 6 or 7 or a pharmaceutically acceptable salt thereof, wherein the carbon atom bearing R^3 and R^4 has the (R)-configuration.

9. A compound as claimed in claim 1 which is selected from

(R)-3-Amino-*N*-((R)-1-benzylcarbamoyl-2-phenyl-ethyl)-4-(2-fluoro-phenyl)-butyramide;

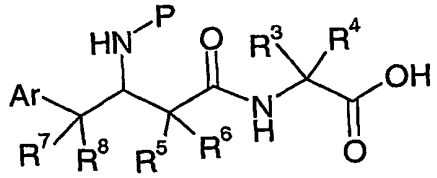
(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-phenyl-ethyl)-butyramide;

(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-[(R)-1-(methylcarbamoylmethyl-carbamoyl)-2-phenyl-ethyl]-butyramide;

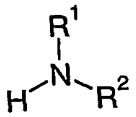
(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-thiophen-2-yl-ethyl)-butyramide;

(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-[(R)-2-(1*H*-indol-3-yl)-1-methylcarbamoyl-ethyl]-butyramide;
(R)-3-Amino-*N*-[(R)-2-(4-chloro-phenyl)-1-methylcarbamoyl-ethyl]-4-(2-fluoro-phenyl)-butyramide;
(R)-3-Amino-*N*-[(R)-2-(4-methyl-phenyl)-1-methylcarbamoyl-ethyl]-4-(2-fluoro-phenyl)-butyramide;
(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-pyridin-3-yl-ethyl)-butyramide;
(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-pyridin-4-yl-ethyl)-butyramide;
(R)-3-Amino-*N*-[(R)-2-(4-bromo-phenyl)-1-methylcarbamoyl-ethyl]-4-(2-fluoro-phenyl)-butyramide;
(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-thiophen-3-yl-ethyl)-butyramide;
(R)-3-Amino-4-(2-fluoro-phenyl)-*N*-((R)-1-methylcarbamoyl-2-pyridin-2-yl-ethyl)-butyramide; and
(R)-3-Amino-*N*-(1-carbamoyl-2-furan-2-yl-ethyl)-4-(2-fluoro-phenyl)-butyramide; or a pharmaceutically-acceptable salt thereof.

10. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1 which comprises
a) coupling of a compound of formula (II) or an activated derivative thereof, wherein P is an amino protecting group, with a compound of formula (III), followed by removal of the protecting group P;

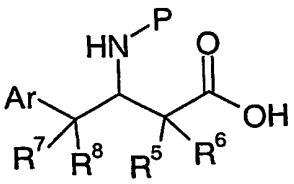


(II)

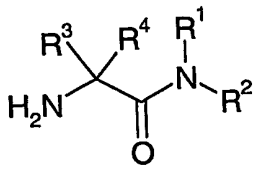


(III)

or b) coupling of a compound of formula (IV) or an activated derivative thereof, wherein P is an amino protecting group, with a compound of formula (V) followed by removal of the protecting group P;



(IV)



(V)

and thereafter if desirable or necessary

(i) converting a compound of formula (I) into another compound of formula (I) using conventional functional group modification; and/or

(ii) optionally forming a pharmaceutically acceptable salt; and wherein Ar, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 have any of the meanings defined in Claim 1.

11. A pharmaceutical composition which comprises a compound of formula (I) or (IA) as claimed in any one of claims 1 to 9 or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable excipient or carrier.

12. A compound of formula (I) or (IA) as claimed in any one of claims 1 to 9 or a pharmaceutically-acceptable salt thereof for use as a medicament.

13 The use of a compound of formula (I) or (IA) as claimed in any one of claims 1 to 9, or a pharmaceutically-acceptable salt thereof in the manufacture of a medicament for use in the production of an inhibition of DPP-IV activity in a warm-blooded animal.